THE SALK INSTITUTE

March 30, 1977

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Dear Aaron,

So pleased to get your letter of the 11 March. The post is so slow (but a little better in the last few days) that it arrived the day after I had read the account of the Royal Society meeting in Nature!

First about Len's work. My point is that the control with a known restriction fragment should be done under exactly the same conditions as those used for the real material. If there are a few nicks in the latter, then they should be filled in with ligase. Alternatively, a few single-stranded nicks should be added to the restriction fragment.

I tend to agree with your assessment of Bak and Zeuthen. Bak seems to me far too fixed in his ideas and not sufficiently critical. I only hope that Zeuthen will turn out to be careful and reliable. I have just today received a letter from Bak telling me that Zeuthen is going to Stockholm in the last week in April to do the mass/unit length measurements. Bak also says that they will try again to get better e/m pictures of the cross-section. It seems to me that establishing these two points is crucial to their story. He says, in passing, that mouse fibres look very much like human ones but that was to be expected. Also that they have prepared fibres with 0.02 M Tris, no hexyleneglycol and only 0.003 M $CaCl_2$ (though that is quite a fair bit) and that they look the same. Bak and Zeuthen are clearly plodding away but I do wish that someone with a little more experience and critical imagination would take up the problem.

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I'm glad to hear the meeting went well. I was sad not to be there but feel I have to keep to my rule not to travel long distances except on infrequent occasions. So far I've been no further than Denver. English people seem to have little idea how far it is even from San Diego to Los Angeles. (It's at least 2 1/2 hours one way by car.) I've twice been up just for a meal. Once to have dinner with Philip Daly (of the BBC) and Dick Feynmann and once to have lunch with Peter Medawar. In future I think people will have to come down here.

Incidentally will you be coming to Cold Spring Harbor -- I assume you will. Also is it possible for you to visit Aarhus while I am there? Unfortunately these absurd tax laws prevent me from coming to England this summer though we certainly plan to do so in the summer of 1978.

I hadn't heard about Chambon's reconstruction using only H3 and H4. Is there any chance of getting 3D crystals of that material? Sometimes these things are easier than one would think. I'd heard about Roger's experiment from someone -- very neat. However, it's still possible that the spacer length varies in some semi-regular way from one spacer to the next one.

Many thanks for Varshavsky's paper. It's clear that they are very active in Moscow but it remains to be seen just what it all implies. As we get more involved with non-histone proteins and "active" nucleosomes, I'm afraid everything is going to get more complicated. Incidentally I look forward to seeing a copy of Joel's paper. The results really should tell us something. Perhaps I should mention that we had a visitor here, Etienne-Emile Baulieu, who has carefully estimated the number of molecules of RNA polymerase B (the one which makes "mRNA", not rRNA) and finds only 8,000 per haploid set for a typical mammalian cell. This is a very small number. You will see that it calculates to about one RNA polymerase B for every 2,000 nucleosomes. So what is all that RNA on Joel's 14S particle, the removal of which turns it so dramatically into an 11S nucleosome?

About Michael Ashburner. He is probably right about the one gene-one band hypothesis but seems to have been carried away a bit. The case he quotes for 3 enzymes (which is probably the rudimentary gene) may occur because one polypeptide chain is produced, containing all 3 enzymes activities, which may or may not be subsequently cleared to give two or three polypeptide chains. This sort of thing may be rather common in eukaryotes. Also my impression is that

between histone genes the "spacers" are rather large -- as much as twice as long as the coding sequences -- and in one case, where the sequence has been done, the "stop" signs are so frequent in the spacer, in all 6 phases, that it's highly unlikely that the spacer codes for a protein. Enough of this sort of spacer may explain George Lefavre's results. (Incidentally he was sitting here in my study half an hour ago!) So, I've decided that what we really want to know, after we have removed special DNAs, like simple sequence DNA, or DNA coding to structural RNA, such as rRNA, tRNA, 5S RNA etc., is: what fraction of the remaining base sequence codes for protein? At least this is a question which we may soon get an educated guess for in Drosophila. Of course, what the non-coding DNA is there for is another matter, but it may pay, in the first instance, to try to find what percentage of the total it is.

About Pardon and Richards. If DNA has about two turns per nucleosome and there are about five or six nucleosomes per turn of a solenoid, then you will easily see that on the simplest model the turns of the DNA on the inside of the solenoid are only 35 Å or so apart, so that one expects a nucleosome to be, if anything, cylindrical or perhaps wedge-shaped, the H1 filling in the "gap" where the sphere isn't -- if you see what I mean. However, I feel only your single crystals can show that. Incidentally, isn't it time you put something into print about them, especially as you have a 3D Patterson. I shouldn't delay too long. In any case I look forward to the internal memo.

As you will probably have heard from Max and Sydney, I have resigned from the MRC from 31 March 1977. I hear that there has been some mention of it in one or two of the London papers, so the Salk is going to make a brief announcement before long. I had delayed them until the MRC had been informed.

Best wishes,

Yours ever,

Francis

F. H. C. Crick
Ferkauf Foundation Visiting Professor

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